REMARKS

All pending claims, namely claims 1-38, stand rejected under 35 U.S.C. § 103 as being unpatentable over Wald, U.S. Patent No. 6,573,103 in view of Stempfle et al. (Pediatric Radiology (1999) Vol. 29, pages 682-688), for the reasons set forth in the Office Action dated September 21, 2006, page 3. No other prior art of record has been relied upon to support the sole outstanding rejection.

Each of Applicants' pending claims include calculating a BPD/OFD ratio of a particular fetus during the first trimester of pregnancy, determining a secondary marker measurement corresponding to the same patient also during the first trimester of pregnancy, and, in combination with the patient's *a priori* risk, assessing the patient's risk of having a fetus with a fetal abnormality. As discussed in more detail below, Applicants' argument can be summarized in three simple points:

1. Stempfle et al. do not teach or suggest using a BPD/OFD ratio during the first trimester of pregnancy;

2. The '103 patent to Wald does not suggest modifying the teaching of Stempfle et al., nor the timing of when a BPD/OFD ratio is determined.

3. Even the prior art of record which has not been relied upon does not suggest using the cephalic index to modify an individual patient's risk.

Therefore, the sole grounds for rejection should be withdrawn.

Stempfle et al. report their results in their Abstract stating, in pertinent part,

> "Brachycephaly was found **as early as 15 WG** in Down's syndrome and continued throughout gestation (sensitivity 0.28, specificity 1)." (emphasis added)

Thus, Stempfle's study was clearly limited to the second and third trimesters of pregnancy. (See discussion in "Materials and Methods" on p. 683 where Stempfle et al. disclose using the cephalic index (BPD/OFD) as a marker for Down syndrome during weeks 15 to 40 in his study, i.e., during the second and third trimesters). The fact that Stempfle et al. were drawing conclusions limited to the second and third trimesters which were the focus of their study is also indicated on page 686 where Stempfle reports

> **"In our study,** the mean value of the BPD/OFD ratio was statistically higher in trisomy 21 compared to the control group, **whatever the GA."** (emphasis added)

The reliance of the Office Action upon the statement on page 683 of Stempfle that Stempfle teaches "at any GA" is not a fair or accurate reading of the Stempfle reference which is limited to weeks 15 to 40. In this discussion of the BPD/OFD ratio on page 683 in Stempfle et al, it is clear that the phrase "whatever the GA" is referring to the second and third trimesters of pregnancy", when this phrase is read in its entirety and in context. This paragraph reads:

> "There was no significant variation of the BPD/OFD ratio with the GA in either group (Fig. 3). **This ratio was nearly constant between 15 and 40 WG. The means of the two groups was greater in trisomic fetuses: 0.879 (δ:0.054) vs. 0.797 (δ: 0.066), P<0.001, whatever the GA**. We

> established a ROC curve for this ratio in the normal group with a confidence interval of 5% (Fig. 4). With this curve, it was possible to choose arbitrarily a threshold value that defined brachycephaly (0.872) according to the choice of
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> sensitivity (0.54) and specificity (0.91). Figure 5 illustrates the cranial morphology in a control and trisomic fetus of the same GA (20 WG)." (Stempfle et al, pg. 683).

Moreover, the reference in this quoted paragraph to Figure 4 supports this interpretation of Stempfle et al, since the caption on Figure 4 clearly states that the reported results are for "the control group". (Stempfle et al., pg. 685).

There is no teaching or suggestion anywhere in the Stempfle et al. reference which suggests using the cephalic index (BPD/OFD) outside of the second and third trimesters of pregnancy.

Wald, U.S. Patent No. 6,573,103 ('103) is not directed to using any new markers nor to using any known markers at times other than during the gestational ages for which those markers were known to be effective. Wald specifically recognized that particular screening markers were known to be effective at different stages of pregnancy. For example, the Wald '103 patent states:

> "Different screening markers generally impart more discriminatory power to a screening test at one stage of the pregnancy than at other stages. Currently employed screening tests rely on certain combinations of biochemical and ultrasound markers that have been identified as being effective when used together at a specific, single stage of pregnancy." (column 1, lines 40-46)

> "The present invention utilizes the fact that the ability of different screening markers to discriminate between Down's syndrome pregnancies and unaffected pregnancies varies according to the stage of pregnancy." (column 2, lines 57-60)
>
> **"Any markers which are effective at each particular stage may be selected."** (emphasis added) (column 5, lines 34-35)

Since Wald does not suggest using any known markers at any stages other than the stages of which such markers were known to be effective, the proposed addition of Wald would not lead one of ordinary skill in the art to modify the teaching of Stempfle et al. to use the cephalic index in the first trimester as presently claimed by Applicants.

The only art of record which mentions using the BPD/OFD ratio in the first trimester indicates that the cephalic index is not an effective marker for the first trimester. Moreover, none of the references cited by Applicants as exhibits with the Response filed on June 30, 3006 teach or suggest using the cephalic index to modify an individual patient's risk as claimed by Applicants. Those references stopped short of providing an actual risk indication for individual patients because:

1. In the case of the Borrell reference (exhibit B), Borrell et al. found

> "In our series, brachycephaly does not appear to be a useful marker, since it is present in 14% of Down syndrome fetuses and in 11% of the controls. A comparison between both groups did not show a significative difference in CI (0.81 vs. 079) (Table 1)" (Borrell, the sentence bridging pages 59-60).

Borrell et al. further concluded that:

> "However, our data show that fetal brachycephaly is not a useful marker for Down syndrome at 13-18 weeks of

pregnancy." (Borrell page 60)

2. Rosati and Guariglia found:

> "the mean CI was 0.82 (97.5% confidence interval 0.72-0.92) in the population with normal fetal karyotypes and 0.82 (97.5% confidence interval 0.77-0.87) in the 36 cases of DS fetuses (p = n.s.). (Rosati and Guariglia, page 39)
>
> Rosati and Guariglia concluded:
>
> **"Our data show that in early pregnancy the cephalic index cannot be considered a useful tool in the detection of fetuses at risk for Down syndrome."** (emphasis added) (see Rosati and Guariglia, Conclusion in Abstract)

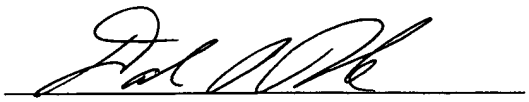
Since none of the art of record which even considered using the BPD/OFD ratio in the first trimester of pregnancy used the BPD/OFD ratio to assess an individual patient's risk or perform a comparison of a BPD/OFD ratio of an individual fetus with observed relative frequency distributions of fetal BPD/OFD ratios from observed affected and observed unaffected pregnancies, the art of record simply does not support a rejection under 35 U.S.C. 103.

CONCLUSION

Applicants respectfully submit that all pending claims, are in condition for allowance. If the Examiner has any questions or comments which might expedite the

prosecution of the present application, she is respectfully invited to contact Applicants' attorney at the phone number set forth below.

Respectfully submitted,



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